

Fetuses of Obese Mothers Develop Insulin Resistance in Utero

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OBJECTIVE — Offspring of obese mothers have an increased risk for obesity and diabetes. The purpose of this study was to determine whether fetuses of obese women have increased obesity, insulin resistance, and markers of inflammation, supporting the concept of fetal programming.

RESEARCH DESIGN AND METHODS — Fifty-three lean and 68 obese women with singleton term pregnancies were evaluated at elective cesarean delivery. Maternal and umbilical cord blood was obtained for measures of insulin resistance and cytokines. Neonatal body composition was estimated using anthropometric measurements within 24 h of delivery.

RESULTS — The fetuses of obese mothers had greater percent body fat (13.1 ± 3.4 vs. $11.6 \pm 2.9\%$, $P = 0.02$), homeostasis model assessment of insulin resistance (1.51 ± 0.86 vs. 1.06 ± 0.70 , $P = 0.003$), cord leptin (14.5 ± 13.5 vs. 8.2 ± 4.7 ng/ml, $P = 0.001$), and interleukin-6 (3.5 ± 2.3 vs. 2.4 ± 1.4 pg/ml, $P = 0.02$) than fetuses of lean women. There was a strong positive correlation between fetal adiposity and insulin resistance ($r = 0.32$, $P = 0.0008$) as well as maternal pregravid BMI and fetal insulin resistance ($r = 0.31$, $P = 0.007$) even with adjustment for potential confounders. Cord leptin had a significant correlation with fetal insulin resistance ($r = 0.30$, $P = 0.001$), but there was no significant correlation between any other umbilical cord cytokines and fetal insulin resistance.

CONCLUSIONS — These data suggest that maternal obesity creates a significant risk for the next generations with metabolic compromise already apparent at birth. Therefore, if prevention of obesity is the goal rather than treatment, the perinatal period may be an important focus of future research.

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The significant increases in adult obesity and type 2 diabetes are clearly public health problems in developed countries and soon will be, if they are not already, significant medical and economic issues in developing countries because of their enormous populations. Obesity and type 2 diabetes are part of a larger syndrome of metabolic dysregulation termed the metabolic syndrome (1). Aggressive treatment later in the course of type 2 diabetes may improve clinical measures such as A1C but unfortunately may not decrease sequelae such as macrovascular complications (2). Unfortunately, the prevalence of obesity continues to increase unabated in adolescent populations

with concurrent metabolic abnormalities (3). The question is then, when should we begin to treat or, better still, initiate preventive measures?

Based on the developmental origins of the health and disease hypothesis or fetal programming (4), the intrauterine environment represents a time when changes in maternal metabolism may affect distant metabolic dysfunction in the offspring mediated through physiological and/or epigenetic mechanisms. Long-term follow-up studies have reported an increase in obesity and type 2 diabetes in offspring of women who are either obese and/or diabetic during pregnancy (5). However, given that ~60% of women of

reproductive age are either overweight or obese (6) and only ~5–10% of pregnant women have a diagnosis of diabetes during pregnancy (7), we have chosen to focus on the greater population risk of maternal obesity affecting long-term neonatal outcomes.

In the last decade, much research has focused on the relationship among inflammation, obesity, and insulin resistance as putative factors for the development of the metabolic syndrome in adults. However, previous reports have indicated that at birth, term infants of overweight and obese women with normal glucose tolerance have increased fat mass in comparison with those of lean or average weight women (8). Because the infants of obese women have an increased risk of adolescent obesity and metabolic dysregulation (9), the objective of these studies was to determine whether at birth neonates of obese women, in addition to increased adiposity, have increased insulin resistance and inflammatory markers. If so, these data would give further support to the concept that the intrauterine environment is a critical epoch for investigation in the prevention of later metabolic dysfunction.

RESEARCH DESIGN AND METHODS

The protocol was approved by the hospital institutional review board, and written informed consent was obtained from each subject. Maternal prepregnancy weight was obtained by history and height measured at the first antenatal visit using a stadiometer. A total of 53 lean (BMI <25 kg/m²) and 68 obese (BMI >30 kg/m²) healthy women with a singleton-term pregnancy were recruited at the time of elective cesarean delivery at term (37–40 weeks) with no clinical evidence of infection. Of the cesarean sections, 113 were elective repeat cesarean deliveries. Seven of the cesarean deliveries were primary cesarean deliveries because of breech presentation (3), a history of inflammatory bowel disease (1), macrosomia (2), and maternal request (1). Normal glucose tolerance was based on a 1-h 50-g glucose challenge test result <135 mg/dl or, if the result was positive, a 100-g oral glucose tolerance test according to the criteria of Carpenter

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and Coustan (10). Maternal blood was obtained on admission for labor and delivery, before placement of an intravenous line for hydration. Umbilical venous blood was drawn via syringe from the double-clamped cord immediately after delivery of the placenta. Plasma was separated by centrifugation and kept frozen at -20°C for glucose, insulin, and cytokine assays. Insulin resistance was estimated using homeostasis model assessment (HOMA-IR) (11). Placenta weight was recorded after trimming of the umbilical cord and fetal membranes by research staff. Neonatal body composition measurements were obtained within 24 h of delivery by one examiner experienced in the technique. The variables included weight on a calibrated scale, length using a measuring board, and abdominal skinfold measures. This methodology has been published previously and correlates strongly ($r^2 = 0.84$) with estimates using total body electrical conductivity (12).

Plasma assays

Plasma glucose was assessed by the glucose oxidase method (YSI, Yellow Springs, OH). Plasma insulin was measured using a radioimmunoassay kit (Linco Research, St. Charles, MO). Leptin and adiponectin were measured using ELISA kits (Linco Research) with intra-assay coefficients of variation (CVs) of 3.0–6.2 and 6.2–8.4%. Plasma tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) were assayed by ELISA (QuantiGlo; R&D Systems, Minneapolis, MN) with CVs of 5.3–7.8 and 2.6–3.4%. Plasma C-reactive protein (CRP) was measured by ELISA (Alpha Diagnostics International, San Antonio, TX) with a CV of 3.0–4.7%. All plasma samples were run in duplicate. The insulin resistance indexes were calculated according to HOMA-IR: (fasting plasma insulin [microcrounits per milliliter] \times fasting glucose [millimoles per liter])/22.5 (11).

Statistical analysis

All values are presented as means \pm SD or in the figures as means \pm SEM. Differences between dependent variables were examined with one-way or two-way repeated-measures ANOVA and adjusted for potential cofounders using ANCOVA. Statistically significant mean differences were identified with a Fisher's protected least significant difference post hoc test. The relationship between maternal and fetal insulin sensitivity was estimated with univariate correlation analysis and ad-

Table 1—Anthropometrics and metabolic parameters of lean and obese mothers and their offspring at delivery

	Lean mothers	Obese mothers	P	Adjusted P value
<i>n</i>	53	68		
Maternal age (years)	28.0 \pm 6.0	27.8 \pm 5.8	0.91	0.51
Prepregnancy BMI (kg/m ²)	22.0 \pm 1.9	38.4 \pm 6.3	0.0001	
Late pregnancy BMI (kg/m ²)	28.2 \pm 3.2	43.0 \pm 6.4	0.0001	
Maternal total weight gain (kg)	16.5 \pm 7.5	11.9 \pm 7.5	0.001	0.008
Maternal net weight gain (kg)	12.8 \pm 7.3	7.8 \pm 7.2	0.0003	0.001
Maternal insulin ($\mu\text{U/ml}$)	11.8 \pm 5.6	26.0 \pm 14.6	0.0001	0.0001
Maternal glucose (mg/dl)	74 \pm 7	79 \pm 11	0.009	0.006
Gestational age (weeks)	38.8 \pm 0.5	38.8 \pm 0.6	0.54	0.57
Birth weight (g)	3217 \pm 452	3320 \pm 460	0.22	0.05
Birth length (cm)	49.1 \pm 1.8	48.9 \pm 1.9	0.63	0.93
Neonatal lean mass (g)	2828 \pm 325	2868 \pm 312	0.51	0.17
Neonatal body fat (%)	11.6 \pm 2.9	13.1 \pm 3.4	0.02	0.001
Neonatal fat mass (g)	384 \pm 150	448 \pm 175	0.04	0.005
Ponderal index	2.7 \pm 0.2	2.8 \pm 0.2	0.004	0.001
Placenta weight (g)	614 \pm 152	693 \pm 184	0.01	0.002
Umbilical cord insulin ($\mu\text{U/ml}$)	7.0 \pm 3.8	9.2 \pm 4.7	0.008	0.02
Umbilical cord glucose (mg/dl)	60 \pm 13	66 \pm 14	0.03	0.07
Smoking status: yes/no	13/40	16/52	0.90	
Hypertension: yes/no/pregnancy-associated	0/53/0	4/60/4	0.04	
Race: African American/Asian/Caucasian/Hispanic	7/1/40/5	29/0/36/3	0.004	
Neonatal sex: female/male	26/27	27/41	0.30	

Data are means \pm SD or *n*. Maternal comparisons were adjusted for race, medical problems, and smoking. Neonatal and umbilical cord measurements were adjusted for race, medical problems, smoking, and sex.

justed for potential confounders using partial correlations. The data were analyzed using the Statview II statistical package (Abacus Concepts, Berkeley, CA) and Statistix 8.0 (Analytical Software, Tallahassee, FL). Statistical significance was set at $P < 0.05$.

RESULTS

Anthropometric and metabolic measures

The anthropometric and metabolic parameters of the lean and obese mothers and their offspring are presented in Table 1. Consistent with their increase in BMI, the obese mothers had a significant increase in fasting insulin and glucose compared with lean mothers. There were no major differences when the maternal analyses were adjusted for maternal race, smoking, or medical problems, such as hypertension. Consistent with what we reported previously in a different cohort, the fetuses of obese mothers had no significant differences in weight or lean body mass at birth, but they had significantly increased fat mass and percent body fat

compared with the fetuses of the lean mothers (8). The ponderal index ([weight in grams divided by length in cubic centimeters] \times 100), a neonatal anthropometric measure of obesity comparable to the BMI, was also increased as was placental weight in the obese cohort. Similar to their mothers, fetuses of the obese mothers had significantly greater fasting umbilical cord insulin and glucose than fetuses of the lean mothers. The results were similar when the neonatal analyses were adjusted for sex, race, smoking, or maternal medical problems, except that the differences in umbilical cord glucose became marginally significant ($P = 0.07$).

Cytokine and inflammatory factors

The obese mothers had increased plasma leptin, IL-6, and CRP concentrations but no difference in circulating TNF- α or adiponectin concentrations (Table 2). There were no major differences when the maternal analyses were adjusted for maternal race, smoking, or medical problems. Because of their increased adiposity, the fetuses of obese women had higher umbilical cord leptin levels than the lean fetuses. Al-

Table 2—Cytokines and inflammatory factors in maternal and umbilical cord plasma at birth

	Lean mothers	Obese mothers	P	Adjusted P value
n	53	68		
Maternal				
leptin (ng/ml)	31.9 ± 20.0	72.1 ± 34.7	0.0001	0.0001
adiponectin (μg/ml)	10.7 ± 4.6	9.7 ± 4.0	0.30	0.39
TNF-α (pg/ml)	1.4 ± 0.9	1.3 ± 0.5	0.67	0.56
IL-6 (pg/ml)	2.4 ± 1.4	4.6 ± 3.4	0.0001	0.0003
CRP (ng/ml)	8074 ± 6467	12433 ± 7918	0.004	0.01
Umbilical cord				
leptin (ng/ml)	8.2 ± 4.7	14.7 ± 13.6	0.001	0.0001
adiponectin (μg/ml)	30.8 ± 10.0	30.6 ± 9.7	0.94	0.71
TNF-α (pg/ml)	1.7 ± 0.6	1.7 ± 0.3	0.90	0.67
IL-6 (pg/ml)	2.4 ± 1.4	3.5 ± 2.3	0.02	0.01
CRP (ng/ml)	121 ± 97	202 ± 286	0.25	0.30

Data are means ± SD. Maternal blood was obtained after an overnight fast at the time of admission for elective cesarean section. Umbilical blood was sampled from the clamped cord within 5 min of placental delivery. Maternal comparisons were adjusted for race, medical problems, and smoking. Neonatal and umbilical cord measurements were adjusted for race, medical problems, smoking, and sex.

though there were no significant differences in umbilical cord TNF-α and a trend for an increase in CRP, umbilical cord IL-6 was significantly greater in obese than in lean fetuses. There were again no major differences when the neonatal analyses were adjusted for sex, race, smoking, or maternal medical problems (Table 2).

Maternal and fetal insulin sensitivity

We estimated insulin resistance in both mothers and their fetuses after an overnight fast at the time of elective C-section using fasting glucose and insulin in the HOMA-IR model (11). The comparison of the HOMA-IR indexes between the lean and obese fetuses and their mothers is shown in Fig. 1A. The mothers were more insulin resistant than their fetuses (P =

0.0001). As expected, the obese mothers were more insulin resistant than their lean counterparts (P = 0.0001). Similarly, the fetuses of the obese mothers were also more insulin resistant (P = 0.003) than the fetuses of lean mothers. As shown in Fig. 1B, there was a strong positive correlation between maternal and neonatal insulin resistance (r = 0.35, P = 0.0002). There was also a positive correlation (r = 0.32, P = 0.0008) between fetal insulin resistance and fetal adiposity (Fig. 2). The relationships were similar in both the obese and lean groups. Maternal pregravid BMI was a significant correlate with fetal percent body fat (r = 0.31, P = 0.0008), but there was no significant correlation between maternal weight gain (r = 0.93, P = 0.33) or increase in BMI

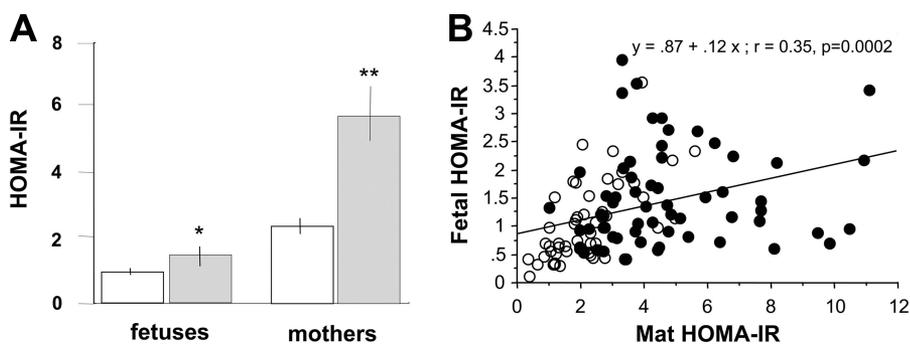


Figure 1—HOMA-IR indexes in fetuses of lean and obese mothers. A: The fetuses of obese mothers have higher HOMA-IR indexes, i.e., they are more insulin resistant than those of lean mothers. The lower HOMA-IR values in offspring compared with mothers are indicative of higher insulin sensitivity in utero. B: Regression analysis shows a positive correlation between maternal (Mat) and fetal insulin resistance. ○, lean (BMI < 25 kg/m²); ●, obese (BMI > 30 kg/m²). Data are means ± SEM. *P < 0.003 and **P < 0.0001 versus lean. □, lean women and fetuses of lean women; ▒, obese women and fetuses of obese women.

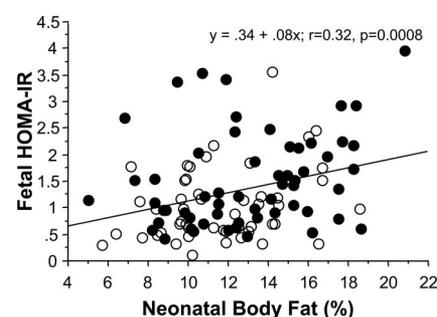


Figure 2—Relationship of fetal insulin with fetal adiposity. Regression analyses show a positive correlation between fetal insulin resistance estimated by HOMA-IR at birth and percent neonatal body fat of the fetus.

(r = 0.11, P = 0.25) with fetal percent body fat.

We next examined the relationship between maternal pregravid BMI and fetal insulin resistance. The positive relationship between maternal pregravid BMI and fetal insulin resistance (r = 0.31, P = 0.007) showed that the more obese the mother is, the more insulin resistant her fetus is. The correlation remained significant (r = 0.27, P = 0.002) after adjustment for the maternal 1-h glucose screening value, race, or maternal medical problems. The relationship of maternal pregravid BMI and fetal insulin resistance also remained significant (r = 0.24, P = 0.003) after adjustment for fetal fat mass or percent body fat.

The adiposity of the fetuses of the lean and obese women in relation to measures of HOMA-IR analyzed as quartiles of percent body fat were next evaluated by ANOVA with assessment of the fetuses in the lowest and highest quartiles using Fisher's protected least significant difference post hoc test. Fetuses of the lean mothers in the upper quartile (15.5 ± 1.5% body fat) had significantly greater insulin resistance (P < 0.04) than that of fetuses in the lowest quartile (8.2 ± 1.3% body fat). Similarly, the fetuses of the obese mothers in the upper quartile (17.3 ± 1.4% body fat) had significantly greater insulin resistance (P < 0.05) than the fetuses in the lowest quartile (8.6 ± 1.4% body fat). Last, there was a significant correlation between umbilical cord leptin and fetal HOMA-IR (r = 0.30, P = 0.001) but no significant correlation between umbilical cord adiponectin, TNF-α, and IL-6 and measures of fetal HOMA-IR.

CONCLUSIONS— Excess adipose tissue combined with low-grade inflam-

mation and impaired insulin action is a central feature of the metabolic dysregulation in adult obesity. Therefore, we asked the question of whether excess adipose tissue during fetal development leads to the same pathophysiologic processes as in adults, resulting in insulin resistance before birth? To the best of our knowledge, our findings are the first to report that fetuses of obese mothers become insulin resistant in utero as estimated by umbilical cord glucose and insulin concentrations.

In neonates, the measures of insulin resistance estimated by clamp studies are low and reflect primarily peripheral rather than hepatic insulin resistance (13), as the enzyme required for gluconeogenesis, phosphoenolpyruvate carboxykinase, does not increase until after birth. Hence, the estimates of insulin resistance in our study are also likely to reflect primarily peripheral and not hepatic insulin resistance. We recognize that there is limited information on the metabolic status of the neonate relative to insulin resistance. Dyer (14), using a minimal model technique, described increased insulin resistance in large-for-gestational-age term neonates compared with that in poorly grown neonates between 24–48 h of birth. Our study measuring insulin resistance in fetuses of fasted mothers (thus, in steady-state glycemic/lipemic conditions) suggests that HOMA-IR is a reasonable estimate of insulin resistance at birth.

During in utero development, the fetus relies primarily on glucose as an energy substrate. There is a steady supply of glucose even during maternal fasting because of the 30% increase in maternal hepatic glucose production in late gestation (15). Maternal insulin resistance during gestation results in increased lipolysis with increased availability of free fatty acids to be used as adipogenic substrates in the fetus. Therefore, understanding the mechanisms through which a fetus growing in a nutrient-rich environment becomes insulin resistant is a major challenge. Fetal hyperinsulinemia has long been accepted as an anabolic factor during in utero development, resulting in fetal overgrowth, particularly in women with diabetes, i.e., the Pedersen hypothesis (16). The recently published Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study reported a strong association between umbilical cord C-peptide and fetal adiposity in women with glucose concentrations less than those for overt diabetes (17). We found similar increases in cord in-

sulin in our study cohort of fetuses of obese pregnant women (Table 1). The anabolic effect of insulin is likely to contribute to an increase in fat mass in utero.

There is a dearth of animal data in this area because of species differences in fetal adiposity, i.e., the human fetus has a greater percent fat mass at birth than fetuses of most other mammalian species (18). Susa et al. (19) showed that implanting an Alzet pump delivering insulin into a fetal rhesus monkey resulted in increased fetal growth including adipose tissue without a change in maternal diet. Our findings again highlight the association between fetal hyperinsulinemia and increased fat deposition in utero. Limited glucose excursions resulting in mild hyperglycemia in obese women with otherwise normal glucose tolerance may be sufficient to modify fetal energy homeostasis.

Is the fetus developing insulin resistance because of excess fat mass? We cannot answer this question directly. We have shown that increased fetal adiposity and fetal insulin resistance are closely associated (Fig. 2). However, maternal obesity had a strong positive correlation with fetal insulin resistance even when adjusted for various maternal confounders including fetal adiposity. These data suggest the possibility of genetic or potential epigenetic factors relating to fetal insulin resistance.

What is most apparent is that fetal circulating cytokines, save for leptin synthesized by fetal adipose tissue, are not correlated with insulin resistance. The increase in umbilical cord plasma IL-6 in the obese fetus may only reflect an increase in total fat mass. Whether there is evidence for inflammation of white adipose tissue in the obese fetus similar to that found in obese adult individuals is not known. Macrophage infiltration of white adipose tissue, however, is present in the white adipose tissue of insulin-resistant children (20).

Our results are in contrast with evidence of inflammation in infants of women with type 1 diabetes (21). Nelson et al. (21) reported that umbilical cord concentrations of CRP, IL-6, and intercellular adhesion molecule-1 were increased and adiponectin concentrations were decreased in infants of women with type 1 diabetes compared with those of control subjects. Although in their study insulin resistance was not estimated, the inflammatory markers in umbilical cord blood were related to measures of umbilical leptin and fetal adiposity. Thus, the relationships of increased adiposity, insulin

resistance, and circulating cytokines in the fetus have yet to be defined.

Based on the developmental origins of the health and disease hypothesis, fetal development in utero may present a particularly vulnerable time period for the maternal environment to affect long-term growth and energy metabolism. We describe here major changes in the metabolic homeostasis of obese women, which alters the environment in which the fetoplacental unit develops. These data are consistent with previous reports characterizing pregnancy in obese women as an inflammatory condition. Stewart et al. (22) also described an increase in IL-6 and CRP in obese compared with lean women in late gestation. Therefore, maternal obesity in addition to the significant 60% increase in insulin resistance of normal pregnancy (15) results in an increased inflammatory state. Most cytokines do not cross the placenta; thus, our results support the concept that maternal inflammation linked to obesity does not directly translate into fetal inflammation (23).

We know that maternal obesity is a risk factor for offspring developing the metabolic syndrome later in life; the question is when does the pathophysiologic process begin? Mingrone et al. (24), in a follow-up study of young adults, reported that the offspring of obese women had significantly greater insulin resistance than offspring of a control group whose mothers had a pregnancy BMI <25 kg/m². Similarly, Boney et al. (9) reported that neonates of obese mothers with normal glucose tolerance had an increased risk of developing the metabolic syndrome at age 11 of almost twofold (1.81, 95% CI 1.03–3.19) compared with neonates of a nonobese group. Last, Whitaker (25) reported that children born to obese women had a 2.5-fold increase of obesity at 2–4 years of age (BMI >95% based on Centers for Disease Control and Prevention criteria) compared with those born to lean or average weight women. Our study extends these reports to the period of prenatal development and emphasizes that fetuses of obese mothers already represent a group at high risk for later disease.

In summary, on the basis of these data we conclude that maternal obesity creates a significant risk for the next generations with metabolic compromise already apparent before birth. If prevention is the goal to stem the epidemic of obesity and related problems, then the perinatal period of development may be an important focus of additional research. Until we at-

tain a better understanding of the underlying genetic predispositions, physiology, and mechanisms relating to maternal and fetoplacental interactions, strategies to counteract the epidemic of obesity must, by necessity, be considered treatment rather than prevention.

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